Hormone Research

Horm Res 2002;58(suppl 3):24–26
DOI: 10.1159/000066478

Fatal Outcome of Sleep Apnoea in PWS during the Initial Phase of Growth Hormone Treatment

A Case Report

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Key Words
Prader-Willi syndrome · Respirational abnormalities · Hypoventilation · Sudden death

Abstract
The case of a boy with Prader-Willi syndrome (PWS) who suffered from respiratory problems since birth and suddenly died at the age of 6.5 years, 4 months after initiation of GH therapy, is presented. This case indicates the possibility of fatal courses in infants and children with PWS as a consequence of respiratory problems and raises the question as to a causal connection between the initiation of GH therapy and the sudden death of this child.

Introduction

Prader-Willi syndrome (PWS), first described in 1956 [1], has an estimated prevalence of 1:5,000 to 1:16,000 [2]. The syndrome is characterized by marked muscular hypotonia and feeding difficulties in infancy. Obesity, short stature, hypogonadism, mental retardation and behavioural difficulties become apparent in childhood. Respiratory abnormalities are well known. An increased incidence of sleep-related breathing disorders has been reported in obese adults with PWS [3–8] and only recently, a primary disturbance of central respiratory control was demonstrated in young, not yet obese children with PWS [9].

The actual link between the chromosomal disorder – mostly deletion or maternal disomy of chromosome 15 – and the clinical symptoms is not yet fully understood. Hypothalamic dysfunction, as already originally presumed by Prader et al., appears to underlie many of the features of PWS, including hypogonadism [10, 11], abnormal appetite control, high pain threshold and sleep disorders, but no overt structural abnormalities of the hypothalamus have been found yet. In recent years, it was shown that growth hormone (GH) deficiency due to hypothalamic dysregulation contributes not only to the abnormal growth pattern and osteopenia, but also to the excess of body fat and to the deficit of lean body mass, with consequently reduced energy expenditure. GH therapy was evaluated in several studies and administration of GH, in combination with restriction of food intake, was shown to have a remarkable impact on growth and body composition, resulting in a dramatic change of the phenotype of affected individuals. Therefore a growing number of children with PWS are treated with exogenous GH. To date, only few potential side effects of GH therapy are known: aggravation of scoliosis or kyphosis [12] under GH-

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0301–0163/02/0589–0024$18.50/0

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induced catch-up growth, accelerated manifestation of type 2 diabetes mellitus in predisposed individuals [13], manifestation of hypothyroidism due to the hypothalamic dysfunction and, most importantly in this particular case, fluid retention in the initial phase of GH treatment [14, 15].

In this paper, we present the case of a prematurely born boy with PWS who suffered from respiratory problems since birth and died suddenly at the age of 6.5 years 4 months after initiation of GH therapy. The aim of this case report is to sensitize paediatricians and endocrinologists to the fact that a subgroup of children with PWS suffering from hypoventilation and other respiratory problems may be at risk for a sudden deterioration of respiratory function at the beginning of GH therapy.

Case Report

The boy was born prematurely at $32^{6}/_{7}$ weeks of pregnancy by caesarean section because of a pathologic CTG and intrauterine growth retardation. Birth weight was 940 g ($p < 3$), length 38 cm ($p < 3$) and the Apgar score 5/7/7. Already shortly after birth, the infant presented with hypoventilation, which was attributed by the physicians in charge to severe hypotonia and muscular hypotrophy of the child. This condition persisted and CPAP treatment and additional oxygen administration proved necessary for the following 6 months. During this time, repeated atelectases of the left lung were striking. Because of the severe hypotonia, PWS was suspected already in the first days and diagnosed genetically (deletion of chromosome 15). During the following 5 months, due to feeding difficulties, the infant had to be fed via a nasogastric tube. A persistent ductus arteriosus had to be operated because of an acute cardiac decompensation at the age of 23 days. At the age of 6 months the boy was discharged from hospital without CPAP, but ongoing oxygen therapy. His weight was 6,050 g (P 3–10) and his length 64 cm (P 3–10).

A cardiologic follow-up at the age of 11 months revealed normal function of the left ventricle and no signs of pulmonary hypertension. Treatment with digoxin and diuretics were stopped. The next 4 years were characterized by rapid weight gain. At the age of 5.5 years, weight had already increased to 24.8 kg (P 90), and the boy had to be hospitalized because of a pneumonia with respiratory insufficiency and subsequent antibiotic treatment. At the age of 5.7 years, the boy was seen for the first time in our institute. Weight had further increased to 27 kg ($P > 97$) and height was 109.5 cm (P 15). He showed typical signs of PWS in a distinct manner. Severe obesity and hypoactivity were present. His developmental delay amounted to about 1 year. In accordance with our PWS study design, GH therapy was started at the age of 6.0 years. Only a short time later, at the age of 6.3 years, the boy suffered a fracture of his left tibia and was hospitalized. At the mother's request, who had noticed episodes of nocturnal apnoeas, transcutaneous O_2 saturation was monitored and significant drops to below 87% were seen, but no further action was taken. A few days later, at the age of 6.33 years, the boy was seen again in our institute. The mother reported that her son snored heavily at night and that, also at home, he suffered from apnoeas during sleep, as seen during the last hospitalization. Following these reports, the physicians in charge were immediately asked to monitor the boy's respiratory function, to perform echocardiography and to initiate CPAP treatment during night. With the parents' consent, GH therapy was continued, because not only beneficial effects of GH on respiratory function described before [16] were seen, but also growth and body composition had already improved. At the age of 6.5 years, an echocardiography showed slightly elevated pulmonary pressure and hypertrophy of the right ventricle. The cardiologist also suggested a nocturnal CPAP or oxygen therapy, provided, however, that other possibilities for an improvement of the respiratory function achieved through interventions conducted by an ENT specialist (e.g. tonsillectomy) had been taken into consideration beforehand. Ten days later, the ENT examination revealed in fact enlarged amygdala and tonsillectomy was proposed as the next step. CPAP therapy seemed indicated to the ENT specialist only after failure of tonsillectomy. Fourteen days later, 3 weeks before the day of the planned tonsillectomy, the boy was unexpectedly found dead in his bed by his parents at 6 o'clock in the morning. No post-mortem examination was conducted.

Discussion

We present the case of a boy with PWS who suffered from respiratory problems since his premature birth and suddenly died at the age of 6.5 years. At the age of 6.0 years, GH therapy was initiated. At the age of 6.3 years, sleeping apnoea with significant drops in O_2 saturation were documented. Before appropriate action was taken, the boy died suddenly in his sleep.

The presented case indicates the possibility of fatal courses in infants and children with PWS as a consequence of respiratory problems and raises the question as to a causal connection between the initiation of GH therapy and the sudden death of this child.

The pathogenesis of the well-known respiratory problems in PWS seems to be multifactorial, including peripheral and central mechanisms, like muscular hypotonia, tonsillar hyperplasia and hypothalamic and chemoreceptor dysfunction [17]. The decreased lean body mass, already present in infants with PWS [18], might be another important factor involved. The resulting decrease in respiratory muscle mass [19], together with a defect in the function and architecture of the throat due to hypotonia, may be the main reason for disturbed respiration leading to an increase of the respiratory drive set-point in the brain stem and to central hypoventilation. Indeed, as shown in two recent studies, GH therapy in children with PWS improves not only lean body mass [20], but also respiratory function [21], leading to an increase in CO_2 sensitivity [16, 22]. In that respect, a causal connection between initiation of GH therapy and deterioration of

respiratory function seems unlikely. However, it is possible that the known GH side effect of fluid retention [15] could outweigh the positive effects during the first months, leading to a fatal course in some children with PWS, who are already suffering from chronic hypoventilation, as in the present case of this prematurely born infant with primary respiratory insufficiency. We recently published another case report of an infant with PWS who died during the first months of GH therapy [23] and we know of a similar case of a boy in Spain (personal communication of the Spanish PWS Association). It therefore cannot be excluded that some children with PWS are at risk for a sudden death in the first months after initiation of GH therapy, most probably because of a right heart failure.

Conclusion

A subgroup of children with PWS suffer from respiratory disturbances with chronic hypoventilation. This subgroup may be defined by additional risk factors, as prematurity (this case) or obesity [14, 23]. They are at risk for the development of pulmonary hypertension. In the case of respiratory infections in these children, monitoring respiratory function and rigorous treatment of the infection is mandatory. If adenoid hyperplasia is present, tonsillectomy can improve respiratory function. In severe cases, CPAP therapy is needed. In our opinion, examination by polysomnography and echocardiography is mandatory in those children, before GH therapy is initiated. In addition, during the first months after initiation of GH therapy, increased awareness for its possible side effects is necessary in order to avoid fatalities as described.

Acknowledgements

We gratefully thank Mrs. Karin Stutz for her help in translating. Our special thanks go to the parents of the deceased child who helped us to reconstruct the case by answering our questions despite being deeply in mourning.

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